

VAUGHAN (V.C.)

THE TREATMENT OF TUBERCULOSIS WITH
YEAST-NUCLEIN.

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BY

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I CLOSED my paper on "The Nucleins and Nuclein-therapy," read before the Michigan State Medical Society last May, with the following paragraph: "I have been using nuclein in the treatment of tuberculosis in man since the 1st of May, 1893. At first I employed only yeast-nuclein, but now I am using spleen-nuclein in some cases. When sufficient evidence has been obtained, either to reject or to recommend the treatment, the results will be communicated to the profession. I may say, however, that only in initial cases may we expect any benefit, and even in regard to these I must have more abundant material and a longer experience before I can speak with any certainty."

Since the reading of the paper mentioned several articles on nuclein and nucleinic acid have appeared, and Professor Kossel, of the University of Berlin, has applied for and has received in Germany a patent on a process of manufacturing nucleinic acid.

In this paper I shall deal only with my own observations and experiments, and, in order that my



statements may be properly connected with those that I have previously made, I repeat the most important conclusions that I have reached and stated in preceding papers. These are as follows :

1. The nucleins and nucleinic acid are powerful germicides. This was first shown in a paper by McClintock, Novy, and myself, published in THE MEDICAL NEWS of May 20, 1893. Additional facts on this point were given in my address before the Medical Section of the Pan-American Medical Congress and published in THE MEDICAL NEWS of October 7, 1893. This work was confirmed in a paper published by Kossel in February, 1894.

2. The germicidal constituent of the serum of blood is a nuclein. This was shown in a paper by McClintock and myself, read at the Pan-American Congress and published in THE MEDICAL NEWS of December 25, 1893.

3. Rabbits and guinea-pigs may be protected against virulent cultures of the diplococcus of pneumonia by previous treatment with hypodermic injections of a solution of yeast-nuclein.

4. The immunity thus secured is not due to the action of the nuclein as a germicide directly.

5. The process of securing this immunity is an educational one, and most probably depends upon the stimulating effect of the nuclein upon some organ whose function it is to protect the body against bacterial invasion.

6. The longer the nuclein-injections are continued and the more frequently they are administered, the more complete is the immunity secured.

7. In order to obtain this immunity, the inocula-

tion with the germ must follow soon after the last treatment with the nuclein.

8. Attempts to render guinea-pigs immune to tuberculosis by the methods so far employed show that previous treatments with nuclein retard, but in the majority of cases do not prevent, the development of tuberculosis from subsequent inoculations.

9. Attempts to arrest tuberculosis already developed in guinea-pigs, by treatment with solutions of yeast-nuclein, have been followed by varying results, depending upon the virulence of the germs used in inducing the disease, the stage of the disease when the treatment is begun, and the susceptibility of the animal, especially as influenced by age. Upon this point we have bestowed much time and labor, but the results have been so conflicting that I am not yet prepared to formulate any positive conclusions. I have in my note-book details of experiments upon more than one-hundred pigs, and I feel that I am as little able to speak positively on the subject as I was when the experiments were begun.

10. I have used nuclein with benefit in the treatment of indolent ulcer, tonsillitis, and streptococcus diphtheria.

The preceding condensed statements bring us to the publication of my last paper on the nucleins, *i. e.*, the one read before the Michigan State Medical Society and published in the *Transactions* for 1894.

Taking up the work at this point, I wish to detail work done upon two other points before I proceed to discuss the results which I have obtained in the treatment of tuberculosis in man with yeast-nuclein.

IMMUNIZING RABBITS TO TUBERCULOSIS.

On March 19, 1894, I inoculated rabbits 1, 2, 3, 4, 5, 6, *a* and *b*, with a virulent culture of the bacillus. Animals from 1 to 6 inclusive had had previous treatments with a one per cent. solution of yeast nucleinic acid, as follows:

March	9,	10,	13,	14,	15,	16,	17,	19
Amt. of sol. } in c.c.	0.3	0.5	0.6	0.7	1	1	1	1

a and *b* had had no nuclein. All of the animals were half-grown, and weighed respectively: No. 1, 714 grams; No. 2, 724; No. 3, 740; No. 4, 729; No. 5, 647; No. 6, 614; *a*, 709; *b*, 705. On July 6, 1894, I killed No. 6, *a* and *b*. No. 6 weighed at this time 1557. I found a nodule the size of a pea at the point of inoculation. In all other respects this animal was normal. I could find no bacilli in the nodule, which was rubbed up with beef-tea and injected into the abdominal cavity of guinea-pig No. 186, weighing 385 grams. On October 10, 1894, I killed this pig, and found a nodule the size of a pea at the point of inoculation. Three small tubercles were found in the peritoneum; the omentum and liver were filled with tuberculous nodules. One testicle was tuberculous.

This is an interesting case, showing that the germ, which had not spread in the rabbit, had, when transferred to the more susceptible pig, induced a widespread tuberculosis.

Rabbit *a* weighed 1030, and *b* 1100 grams. In both nodules as large as filberts were found at the point of inoculation, and smaller nodules in the omentum. On October 10th I killed No. 1, weight 2134. This animal was found to be wholly free from tuberculosis. On October 4th I killed No. 2, weight 2150,

which was found perfectly normal. No. 3 was found dead October 2. Post-mortem examination showed a pear-shaped tumor in the omentum. This tumor was three inches long and one-and-a-half inches in diameter at the base. It consisted of three cysts, which contained very fetid pus, in which were found a short bacillus and a large micrococcus. There was no evidence of tuberculosis. No. 4 was killed October 10th, weight 1990. I found a small nodule at the point of inoculation. This was not attached to the abdominal wall, but was in the connective tissue, between the skin and the muscle. I could find no germ. In all other respects this rabbit was normal. No. 5 was killed October 10th, weight 2000, and found perfectly normal.

These experiments indicate that rabbits may be rendered immune to tuberculosis by previous treatments with yeast nucleinic acid.

THE TREATMENT OF RABBITS WITH NUCLEIN.

On May 26, 1894, I inoculated rabbits 1, 2, and *a*, intra-abdominally with a pure culture of the bacillus tuberculosis. Their respective weights were 657, 685, and 547 grams. Nos. 1 and 2 had daily, from May 28th to July 3d, 0.5 c.c. of a 1 per cent. solution of yeast-nucleinic acid; *a* had no treatment. No. 1 was killed October 11, 1894, weight 1390, and found normal in every respect. No. 2 was killed October 11th, weight 1530, and was found perfectly normal. Rabbit *a* was killed October 11th, weight 990 grams. A nodule as large as a filbert was found in the peritoneum at the point of inoculation. There were many millet-seed nodules in the peritoneum and omentum, one in the left kidney, two on the walls of the abdominal aorta opposite the left kidney, several on the peritoneal

covering of the greater curvature of the stomach, a tuberculous mass on the smaller curvature of the stomach, and the liver was dotted with pin-point nodules.

June 8, 1894, I inoculated intra-abdominally rabbits 1, 2, 3, 4, 5, 6, 7, and *a* and *b* with a pure culture of the bacillus tuberculosis. These animals were only a few weeks old, and their respective weights were respectively 365, 335, 327, 405, 415, 430, 385, 350 and 375 grams. No. 1 had daily,¹ from June 11th to September 25th, 0.5 c.c. of $\frac{1}{2}$ per cent. of yeast nucleinic acid.

No. 1, now weighing 1337, was killed October 5th. Examination showed no abnormality. Nos. 2, 3, 4, 5, 6, and 7, having had the same treatment as No. 1, were also killed October 4th. Their respective weights were 1400, 1410, 1295, 1425, and 1395 grams. No. 2 had coccidia in the liver, but no tuberculosis. No. 3 was normal. No. 4 had a millet-seed tubercle in the right inguinal region. This contained bacilli. No other abnormality could be found. No. 5 had a millet-seed nodule in the omentum, in which no germs could be found. Otherwise it is normal. No. 6 had coccidia in the liver, and one pin-head tubercle in the omentum, in which no germs could be found. Otherwise it was normal. No. 7 was normal in every respect.

Rabbits *a* and *b* were killed October 5th, their respective weights being 1488 and 1320 grams; *a* had a tuberculous nodule as large as a cherry-seed

¹ The statement that these treatments were given daily needs some modification. My assistant, Mr. Perkins, who administered these treatments, gave up his vacation to the work, and, had it not been for his untiring perseverance and sacrifice of time and labor, I could not make this report. But he could not attend to this every day, and during the time mentioned there were eighteen days in which no treatment was given.

at the point of inoculation, and numerous smaller ones in both the greater and smaller omentum. The liver contained several nodules as large as split peas, and a few were found in the diaphragm. The right kidney was tuberculous. *b* showed diffuse tuberculosis in the abdominal walls for one-half inch around the point of inoculation. There were two nodules in the omentum, and the liver was thickly dotted with pin-point tubercles. The other organs were normal.

These experiments convince me that when the treatment is begun within three or four days after the inoculation, the development of tuberculosis in rabbits may be prevented by yeast-nucleinic acid. These experiments will be repeated, and the length of time between the inoculation and the beginning of the treatment will be increased.

YEAST NUCLEINIC ACID IN TUBERCULOSIS IN MAN.

In reporting my observations on this point, I am beset with certain difficulties. In the first place, the solutions used during the first six months were by no means free from other proteid material, and the exact amount of nucleinic acid in them was not known. In the second place, I had an idea in the first part of my work that the efficiency of the nucleinic acid would be increased by administering it in a strongly alkaline solution. This idea was founded upon the experiments of Fodor, who has shown that certain animals are rendered partially immune to anthrax by increasing the alkalinity of the blood. However, a condition may be protective to an animal against one disease, and without

influence, or even detrimental, in another disease. McClintock has recently made one series of experiments in which a number of tuberculous guinea-pigs were treated with hypodermic injections of a solution of sodium carbonate, while others inoculated at the same time with the same sputum were left without any treatment whatever. The results showed not only that the treated animals died before the untreated ones, but the treated ones showed a much more extensive tuberculosis than we have ever before observed in animals dying from inoculation-tuberculosis. These experiments will be repeated, and should the results be confirmed we must conclude that the administration of an alkali diminished rather than increased the efficiency of the nuclein-treatment.

In the cases most recently treated I have, of course, attended to many details that I have ascertained to be important, and of which I was formerly ignorant. Moreover, I have improved the preparation of the nuclein. I also now refuse to employ the remedy in advanced cases in which I know it can be of no service. By carefully examining the sputum of every person who comes to me with a cough, and by testing every sample of urine that contains any pus or blood¹ for the bacillus, I have detected the presence of the disease in its earlier stages. Consequently, the results obtained during

¹ Since writing the above we have detected tubercle-bacilli in urine in which there was neither pus nor blood. The patient had suffered from severe pain in the left kidney and along the ureter, and the trouble had been diagnosed, and was treated as one of renal calculi.

the past twelve months have been more satisfactory than those of the earlier months.

CASE I.—A. W., was born in Ann Arbor, of German parents, in 1869. His father and mother were living at the time the treatment was begun, and no member of the family had given any evidence of tuberculosis. He had been employed in a drug-store for nearly ten years, the last three years at Calumet, Michigan. For the past four years, possibly longer, he had been drinking excessively. Dr. Pomeroy, of Calumet, sent him to me about the first of April, 1893. At Christmas, 1892, he weighed 138 pounds. About this time his cough attracted the attention of Dr. Pomeroy, who examined his sputum and found tubercle-bacilli present in large numbers. During the first four months of 1892 the disease made rapid progress. During April the evening temperature ranged from 102° to 103° . The man took from one-fourth to one-half grain of morphin each night to allay the cough. Night-sweats were constant, profuse and exhausting. During this time he staid in doors, and the hygienic condition of the house in which his parents lived, and where he staid from his coming home until his death, was extremely bad. Situated on low ground, without cellar, heated by stoves, unventilated, and damp, it furnished a most unsuitable abode for the patient. I recognized this fact all the time, but being unable to change his habitation, I thought that the results, whatever they might be, would be interesting, inasmuch as I would learn what could be done under such unfavorable conditions. On the first day of May, 1893, I began the nuclein-injections, and I insisted that however he might feel, or whatever the weather might be, he should walk to my office, a distance of about half a mile, every morning, and that in good weather he should be

out of doors as much as possible. On this day he weighed 113 pounds. The use of morphin and all other drugs was prohibited. The upper third of the left lung and the apex of the right contained small cavities. The cough was severe and the expectoration measured half a pint or more daily. During the first three weeks of treatment he was compelled to rest several times on his way to the office each morning. The solution used contained 0.9 of one per cent. of impure yeast nucleinic acid, and 0.25 per cent. of potassium hydroxid. The injections were at all times made in the muscles of the chest. I began with three minims of this solution, and gradually increased the dose to eighty minims. The temperature, which was taken three times a day, with a tested thermometer, rapidly fell until May 12th, when it was normal all day. From this time until August 31st the maximum temperature was not above 99° , with the following exceptions: June 1st, he had a sharp diarrhea and an evening temperature of 100° . June 16th, he had an evening temperature of 101° , followed by a profuse sweat. July 13th and 14th he had a temperature of 100° , following unusually large injections of the nuclein. On July 21st his midday temperature was 101° , and the following day 100° . During these days he had no injections, but he took a solution of nuclein containing 0.5 per cent. alkali three times daily in tablespoonful doses. This was discontinued and the temperature became normal. August 4th and 11th, he had an evening temperature of 100° without any assignable cause. From August 21st to 25th he had a diarrhea, of unknown cause, and twice during this time the temperature registered 101° . August 29th, the temperature went to 100° after an injection.

The man's weight gradually increased, some weeks losing a little, others gaining, until August 31st he

weighed 119 pounds. The cough and expectoration gradually decreased until my last August record on this point, which is as follows: "August 19th, examined the sputum. The amount is very small. He brought all that he raised this morning, not more than a teaspoonful. Before the treatment was begun he would cough and raise all night, unless he had a large dose of morphin. The sputum, however, though small in amount, is rich in germs."

I could not see that during this time there had been any marked alterations in the physical conditions, except that there was an absence of râles over the involved areas. The patient could now run two or three blocks without getting short of breath, but the cavities were still there. I should say that from May 12th to August 31st the progress of the disease was arrested or so modified that its advance could not be detected. I must admit, however, that I cannot speak with the confidence that some do concerning very slight alterations in the lungs as determined by physical signs.

From August 31st to September 12th I did not see the patient, although I provided for the continuance of the treatment through the kindness of my colleague, Dr. Clark, who did his duty thoroughly. But the patient took this time, as I afterward learned from his mother, to go on a protracted spree. She reported that he was frequently out at night until very late hours, and that more than once he came home intoxicated.

After my return he had only a few treatments, and some weeks passed without my seeing him. Late in October, the sickness and death from typhoid fever of another member of the family depressed him very much. He began the use of morphin again, and a return of the high temperature, frequent cough and abundant expectoration showed the rapid progress

of the disease. The last injection was given September 29, 1893, and he died March 17, 1894.

Just how much of the temporary improvement which accompanied the nuclein-treatment was due to this I cannot say. I am inclined, however, to attribute no small part of it to the temporary abandonment of bad habits and the getting out of doors, which took him for a considerable portion of the twenty-four hours from the unsanitary house. Moreover, open doors and windows during the summer reduced the ill-effects of his unsanitary surroundings to a minimum. I am glad to report this case, because it plainly teaches, in my opinion, that the sanitary conditions of the domicile and the habits of the patient are important factors in the treatment of tuberculosis. I believe that they are of much greater importance than climatic conditions.

CASE II.—F. M., a student from Kansas City, aged twenty-two; knew of no tuberculosis in the family. He had his first hemorrhage in 1891, and has had several recurrences since, the intervals becoming shorter. He had a quite profuse one six weeks before, and another the day before he first consulted me, which was late in April, 1893. He had weighed 125 pounds the preceding Christmas; his weight at the time of beginning treatment was 115½ pounds. Moist râles were heard over both lungs both anteriorly and posteriorly. No cavities could be detected. The sputum contained numerous tubercles half the size of peas. On crushing these between cover-glasses and straining, each was found filled with bacilli. The daily maximum temperature for three days before beginning the treatment

averaged 100.3° . He had had a night-sweat every night for some weeks.

Treatment was begun May 1, 1893. The same solution in the same quantities as in the preceding case was used. The last treatment was given June 30, 1893. The temperature did not reach 100° after June 2d; it seldom went higher than 99° , and during the last four days it was normal continuously. The râles disappeared, and diminished resonance over the upper lobes was the only physical evidence of the diseased condition. During the treatment there was no gain in weight, the record for June 24th showing $114\frac{1}{2}$ pounds. Night sweats were occasional and slight during June. The cough and expectoration decreased, and some mornings during the latter part of June he failed to raise anything when asked to bring the sputum for examination; but when sputum was raised and examined, the bacillus was always found.

After leaving Ann Arbor he spent one week at the World's Fair, and then went home. A letter of July 10, 1893, states that his cough had been very infrequent, and the highest temperature observed was 99° , though it was taken somewhat irregularly. Later in the same month the young man, accompanied by his father and brother, drove in a light wagon from Kansas City to Boulder, Colorado, where a position had been tendered him, and where he has since lived. During this journey he lost some flesh, weighing 111 pounds after reaching Boulder. Since that time he has very slowly gained in weight, having increased to 125 pounds in June, 1894, when he visited Ann Arbor. I examined him carefully at that time, and could not detect any marked alteration in the physical signs from those observed one year before. He seldom coughed, sometimes not for several days, but when he did raise anything I

could easily find the bacilli. He calls himself well, but the infection remains. He has had no nuclein since June 30, 1893. It is impossible to say whether or not the improvement would have continued, or whether or not the bacilli would have remained, had the treatment been kept up. To attempt to answer these questions would be to theorize, and this would be neither scientific nor profitable.¹

CASE III.—H. H., a student from Silver Springs, N. Y., had been home during the spring vacation of 1893, and returned with a letter from Dr. Straight, of that place, to me, in April. He was twenty-four years of age, and his usual weight had been for some time 140 pounds, but the first day of May his weight was 127. His maternal grandfather was said to have died of pulmonary tuberculosis, but he knew of no other case in the family. He had never seen this grandfather. His father and mother were living and well. He had had a hemorrhage in the spring of 1892, but during the early winter of 1892-93 he had felt especially well. However, during the latter part of this winter he had felt depressed and weak. Late in March he had another hemorrhage. The upper lobe of the left lung was extensively involved, and contained a large cavity. The apex of the right lung contained a smaller cavity. The evening temperature averaged 100.4°. Cough and expectoration were free, and the sputum consisted of a purulent fluid containing numerous tubercle-bacilli. The patient was very weak, and should have been compelled to discontinue his work, which was that of a student in mechanical engineering, demanding considerable exertion, but he was to graduate in a few weeks, and insisted on continuing his labors. He had the same treatment as the pre-

¹ Since writing the above I have learned that Mr. F. M. had several hemorrhages recently.

ceding two, taking his last injection July 7, 1893. During this time he gained three and one-half pounds, and during the last week of his stay here his daily maximum temperature averaged 99.4° . There was no detectable alteration in the physical signs, and the sputum remained substantially the same. He then returned to his home in New York, where he took cod-liver oil and malt. For some weeks he sent me a daily record of his temperature. The average maximum was 100.5° for the week ending July 28th. After this he was for eight weeks in a sanitarium at Lakewood, New Jersey. He also sent me a partial record of his temperature while there, but as he was taking antifebrin whenever the temperature rose to 100° , the record is of no value. On his return from the sanitarium to his home he sent me some of the sputum, in which I found no evidence of improvement. In February, 1894, he sent to me for some nuclein to be used by Dr. Straight, but a letter from the doctor told me he regarded the case as hopeless. However, he did use the nuclein for some weeks, but the disease progressed, and death occurred October 1, 1894. I do not believe that the nuclein could have been of any material benefit in this case had it been continuously employed.

CASE IV.—Dr. M., aged twenty-six, consulted me June 21, 1893. At my request he wrote at that time the following short history of his case: "In February, 1892, I was not feeling well, and attributed this to the want of exercise, as I was closely confined in the laboratory, but had no symptoms to attract attention to the urinary tract. One day, while examining various urines, I accidentally discovered pus in mine. I took boric acid, then salol, pichi, and lastly buchu, without effect. Stone was suspected, and Dr. Nancrede passed a sound with negative result; but after the sounding the

urine became almost normal, and remained so for several weeks, then gradually became as cloudy as ever. In July, 1892, Dr. Warthin discovered tubercle-bacilli in small caseous masses deposited in the urine. I then took a capsule containing one grain each of quinin and iodoform and one-thirtieth of a grain of strychnin sulphate, three times daily, from August, 1892, to February, 1893. I took also during this time six bottles of malt. During August and September, 1892, I used injections per catheter of iodoform in oil, but this set up such a violent inflammation that I desisted from all local medication. In February, 1893, my appetite completely failed, and thinking that the iodoform caused this I discontinued it. Then I began hypodermic injections of iodine and gold, taking at the same time about two ounces of cod-liver oil per day. I took during February, March, April and May, 1893, about sixty injections of iodine and forty of gold, ten minims in each injection. The cod-liver oil became nauseating, and had to be discontinued, after having taken about one gallon in seven weeks, and gaining seven pounds. My weight when bacilli were discovered in July, 1892, was 119 pounds; in September, 124 pounds. After taking the cod-liver oil my weight reached 131, but soon fell after discontinuing the oil, and now it is 122. I have never had night-sweats, or rise of temperature. My appetite is good, but my bowels are constipated. The local symptoms are scarcely noticeable, but there are slight irritation and pain in the perineum on urinating."

A few days ago I wrote to Dr. M., who is now practising in Nebraska, and asked him to give a short synopsis of his case from beginning the nuclein-treatment to the present time. I insert his answer without alteration:

HEMINGFORD, November 16.

"Yours of the 16th instant to hand this morning, and I enclose an account of my past and present condition. I keep nuclein on hand all the time, and it promptly relieves any vesical irritation. I have used it with marked benefit in two cases of pulmonary tuberculosis—one is now quite well, the other is dead. I used it with good effect in several cases of acute naso-pharyngeal catarrh. My own health I consider as fully restored. On June 21, 1893, I had first injection of nuclein, about 5 mg. On June 22, 23, and 24 I had increasing doses, and June 25 had 25 mg., which caused severe local inflammation, chill and fever.

On June 28th, I had another small injection. On June 30th I went to Manistique, Mich. My weight then was 121½ pounds. On July 12th I began the use of nuclein, 4 c.c. per day hypodermically, and continued for four weeks, when I weighed 124½ pounds. At this time I had a severe attack of diarrhea. On August 18th. I received more nuclein, which I used as before until about September 12th, when I left Manistique and went to Chicago for two weeks. On September 26th I returned to Ann Arbor and again used nuclein hypodermically, from 6 to 12 c.c. per day. On October 4th I commenced injecting directly into the bladder about 2 oz. nuclein plus 2 oz. normal saline, after first washing out the bladder with normal saline solution. My weight was 119 pounds. I had so much irritation of the bladder that I had to take tincture of hyoscyamus constantly. I injected nuclein hypodermically twice a day and into the bladder once or twice a week till about November 26th. I used only vegetable diet. My weight was 123½ pounds. I had to discontinue injections into the bladder on account of irritation. I had much stomach-trouble, and on December 23d I weighed 118½ pounds. On December 23d I discontinued all injections and

took nuclein only by the stomach, about 3 or 4 oz. per day. I took also iron and ergot for two weeks. I changed diet from vegetable to chiefly proteid food, and took a little cod-liver oil, which disturbed the digestion. On January 6, 1894, I felt much better. Irritation of the bladder had ceased, digestion was much improved, and my weight was 120 pounds. On March 14th, the bladder was very irritable, and incontinence of urine was very troublesome. I had to use a rubber urinal. I used nuclein hypodermically and also injected it into the bladder. I took uva ursi for vesical irritability. On April 4th I left Ann Arbor for Nebraska. The bladder was very painful, and urine could not be retained for more than two or three hours at any time. My weight was 118 pounds. On June 15th I had improved very much. I have used altogether four gallons of nuclein-solution, mostly injected into the bladder. I had no incontinence and very little irritation of the bladder. The urine still contained pus. My weight was 125 pounds. On July 27th I had a severe attack of acute cystitis, lasting three weeks, and I passed a small phosphatic calculus about a quarter of an inch in diameter, after which the cystitis rapidly improved and soon ceased entirely.

November 19th. Since July I have steadily improved, and have used no treatment of any kind except an occasional injection into the bladder of an emulsion of iodoform. I have no incontinence and scarcely noticeable irritation. I am feeling better generally than during any time the past ten years. I am heavier than for twelve years and have gained $7\frac{1}{2}$ pounds in the past two weeks. The urine is still slightly cloudy, mostly from mucus, as there is little pus. I sent a sample to Dr. Warthin last week to be examined for tubercle-bacilli.

A. L. MUIRHEAD.

Dr. Warthin reports that he could find no tubercle-bacilli in the urine.

CASE V.—G. T., aged twenty-two, first consulted me in October, 1892. At that time he had considerable irritation at the neck of the bladder, frequency of micturition, and a deposit of blood in the urine. He was sent to Dr. Nancrede with the request that he be sounded for stone. Dr. Nancrede failed to find a stone and suggested tuberculosis. Examination showed tubercle-bacilli abundantly present in the urinary sediment. Salol, quinin, iodoform, and other remedies were tried, both internally and by injection into the bladder, but the progress of the disease was in no wise arrested. In the spring of 1893 T. went to Colorado. He remained in the West, in Colorado and New Mexico until the first of April, 1894, when he returned to Ann Arbor to try the nuclein-treatment. Evidently his stay in the West had not retarded the progress of the disease. When he went West the disease was confined, so far as the symptoms indicated, to the bladder. On his return the left kidney formed a tumor as large as the head of a newly-born child, and could be plainly felt through the thin walls. Nearly every day he was compelled to take morphin in order to allay the severe pain due to the passage of tuberculous masses from the kidney to the bladder. This pain came on in paroxysms, and often seemed as severe as that due to the passage of calculi along the ureter. The urine contained a large amount of pus and blood, in which tubercle-bacilli were easily detected. Sleep was often prevented by the pain. With the exception of the bladder and kidney there was no evidence that other organs were involved in the tuberculous process.

The nuclein-injections were begun April 12, 1894, and with a few exceptions they have been

continued daily from that time to the present writing (November 20). A one-half per cent. solution was used until about the middle of October, since which time a one per cent. solution has been employed. Ten minims constituted the first dose, and the amount was rapidly increased to eighty with the weaker solution and forty with the stronger. The injections are made deeply into the muscles on each side of the spine, over the kidneys. There is no evidence of enlargement of the right kidney, and the greater number of the treatments have been given on the left side.

The greatest weight reached before his illness was 132 pounds. The decrease was gradual and constant to the time of beginning the treatment, when he weighed 114 pounds. Since beginning the treatment the weight has steadily increased and is now 138 pounds. The temperature at first often reached 102.5° and sometimes 103° in the evening. It has not been above the normal since early in October. The urine will be wholly free from sediment for several consecutive days, and then there will be a little pus in which the bacilli can be detected. There is still some undue frequency of micturition, and at times a sensation that the bladder has not been wholly emptied at the close of the act. The kidney has decreased in size but is still abnormally large. There has been no pain from the passage of tuberculous masses through the ureter since the latter part of May. Of course, it is possible that the disease may extend again. I shall not call this a cure until the urine becomes permanently normal, and this may never happen. But even should this not occur, the history of the case is unique.

CASE VI.—This case is reported out of order chronologically, in order to bring together the

cases of urinary tuberculosis which I have treated with nuclein. R., a physician, practising in Wisconsin, ordinarily very robust and weighing about 200 pounds, aged forty-three years, had not been feeling usually vigorous for some months, and had lost about 15 pounds. In February, 1894, he noticed traces of blood in his urine. Some of this was sent to me for examination. The tubercle-bacillus was detected and a guinea-pig was inoculated with the sediment. Twelve days later, Dr. R. came here, and both of us being anxious to know whether or not the microscopic finding would be confirmed by the inoculation-experiment, the pig was killed. There was a tuberculous nodule containing bacilli at the place of inoculation, and two smaller ones in the peritoneum. The next day, March 19th, the treatment was begun. There had been no elevation of temperature before this, and a general feeling of lassitude and the deposit in the urine were practically the only things to attract attention. Ordinary doses of nuclein were followed in this case by a marked elevation of temperature, so that after the first few weeks not more than 30 minims were given. The deposit wholly disappeared in a short time. The injections were continued up to August, since which time no treatment has been used. The lost flesh has been regained and the urine remains normal. Evidently, in this instance, the disease had not progressed very far.

CASE VII.—Mrs. Z., came to me June 25, 1893. Her condition was bad. She had a large abscess from pyosalpinx, from which an umbilical hernia resulted. The left lung was involved throughout its entire extent and contained a large cavity in the upper lobe, and the upper lobe of the right lung was consolidated. She had been treated for some months with injections of gold and iodin. Her

weight was 117 pounds. The treatment was begun June 25, 1893, and was continued to September 19th of the same year. Although there was some slight gain in weight (to 123 pounds), the disease steadily progressed. In September she went to Arizona, where she remained until June, 1894, when she returned to Ann Arbor, and, failing constantly, died early in September.

CASE VIII.—Mrs. C., had been known to have “consumption” for two years. Her weight was reduced to 80 pounds, from 115 in health. Both lungs were filled with cavities. The evening temperature ranged from 102° to 103° . Nuclein was used two or three times per week without the slightest effect.

CASES IX to XVI inclusive were all instances of extensive involvement and with cavities. A detailed report of these would not be of special interest. Suffice it to say that although there were in some marked evidences of temporary improvement while under treatment, the disease, on the whole, has progressed. I am not inclined to attribute the temporary improvement in these cases to the treatment. One who has had any large observation of this disease knows how often these false promises are made under all forms of treatment and even when no medication is employed.

CASE XVII.—A. W., a colored man, a student, who is paying his way through college by acting as general servant in a fraternity house, came to me for examination and treatment June 5, 1894. He was then twenty-five years old and weighed 140 pounds. In the spring of 1893 he weighed 154 pounds. He went to the World's Fair, and thinks that he “took cold there.” He began to cough, lose weight, and have a “tired feeling.” When he came to Ann Arbor in October, 1893, he weighed

148 pounds. He had been coughing quite violently for six weeks before he consulted me. His mother and one brother died of pulmonary tuberculosis, the first many, the second, three years ago. He had had sharp pains in the lower lobe of the left lung for some days, and this had caused him to consult a physician. The upper lobes of both lungs are filled with moist râles, and there is a pleuritic effusion on the left side. I am not sure about cavities; if any, they are small. The sputum was abundant, purulent, and filled with tubercle-bacilli. Guinea-pigs were inoculated with the sputum and died from tuberculosis in from four to six weeks. His evening temperature for some days after beginning the treatment was 100°. W. continued his duties as a servant and his studies until the close of the college year in June last. In July he went to the Oakland Hotel, at St. Clair, where he acted as waiter and general servant during the season. He returned to Ann Arbor in October and took up his work again. He has not lost a day from his work during this time. The conditions under which he lives are not the most favorable for one in his condition.

The injections were begun January 5, 1894, were continued until the close of the college year, were occasionally administered by Dr. Burtless at the Oakland during the summer, and were resumed by me on his return to Ann Arbor in October. From the beginning until October a one-half per cent. solution of nucleinic acid was employed, and latterly a one per cent. solution. The injections have all been made into the muscles of the back, and in amount have averaged about thirty minims.

He now weighs 140 pounds, just what he did when I began the treatment, though he continued to lose for a while, and reached the lowest point, 132 pounds, about three weeks after beginning the treatment.

The pleuritic effusion disappeared in a few days, and the moist râles in as many weeks. His evening temperature fell about one degree, and has averaged about 99° ever since. The amount of sputum is now small, but it contains bacilli. There is lessened resonance over the upper lobes on both sides, but there is no evidence that the disease has progressed. He works hard, sleeps well, looks and feels well, but he is still infected.

I believe that in this case the progress of the disease has been retarded by the treatment—I will not say arrested, because so long as the infection remains there also remains the probability that it may at any time become progressive.

CASE XVIII.—E. W., aged twenty-three, a book-keeper in a bank at Chelsea, Michigan, consulted me February 19, 1894. His mother had a cough for some years before her death, which occurred in 1886. His father is living and well. He has no brother or sister. In the spring of 1893 he weighed 140 pounds; his weight at time of first examination was 134 pounds. He had been coughing and raising abundantly since the last of August, 1893. He passed an examination for life-insurance September 6, 1893. This, however, is no proof that he was sound at that time. The expectoration was very abundant, thin, purulent, and contained numerous bacilli. There was a small cavity in the upper lobe of the right lung, and an extensive pleuritic effusion upon the left. Some of this effusion was drawn with a needle and found to contain tubercle-bacilli.

Treatment was begun February 19, and has been continued with occasional interruptions until to day, November 23. The kind and amount of nuclein-solution used were the same as in the preceding

case. This young man has continued his work, getting at it early and leaving it late. In addition to his work, he has come to Ann Arbor, a distance of eighteen miles, daily, except Sunday, for treatment. This he has done through all kinds of weather, sometimes waiting until late at night for the return train. Surely these conditions have not been most favorable.

In this case the pleuritic effusion was very slow in disappearing, and to-day there is diminished resonance over the left lung. I cannot see that there has been any material change in the upper lobe of the right lung. The sputum is not so abundant, but the relative number of bacilli has not been altered. The temperature varies with the amount of work which the patient does. When he is very busy, the evening temperature goes as high as 102° . When he has a day of rest it seldom rises above 99° . This has been the case all the time, though the average temperature is higher now than it was last February, and, judging by this more than by the physical signs, I think that the disease is slowly progressing. His weight now is 135 pounds.

CASE XIX.—Miss H., twenty-seven years old, a saleslady in a dry-goods store, consulted me December 31, 1893. Three years before she had weighed 146 pounds, had been gradually losing, and at the time of examination weighed 115 pounds. She had been coughing and raising "a little" in the morning during these three years. She had no night-sweats. There is no family history of tuberculosis. The upper portion of the upper lobe on the right side was consolidated, and moist râles were heard over the upper lobe on the other side. The sputum was not purulent, but contained tubercle-bacilli.

The treatment was begun January 4 and continued daily until the middle of July, when it was given

twice a week, and since the 1st of October once a week. The average daily maximum temperature was, during the first six weeks, 99.8° ; then it gradually fell to the normal by March 5th, and since that date no elevation of temperature has been found, with one exception, although observations were made, with occasional lapses, three times a day. The germs in the sputum, which was tested once a week as long as there was any, gradually decreased, and the first record of "no tubercle-bacilli" was made March 28. None has been found since. November 14 Miss H. had quite a sharp attack of bronchitis, with a temperature of 101° , cough, and expectoration, lasting through three days. This sputum was most carefully examined for tubercle-bacilli, with negative results. The weight has gradually increased and has reached 126 pounds. Miss H. discontinued her duties as a saleslady from the beginning of the treatment until May 1st, since which time she has been at work. In taking the treatment she walked daily, without reference to weather, from her home to my office, a distance of about one mile, and back. Did I not know that her lungs had been infected I do not think that I would be able to detect any evidence of it from a physical examination.

CASE XX.—Miss W., aged twenty-three, first consulted me February 12, 1894. She is of German parentage. Her father's family was said to be "consumptive," though the father died three years ago of chronic nephritis. The mother is not robust, but has never been sick. She has one brother twelve years old, who is well. During the spring and summer of 1893 Miss W. did not feel well and declined in weight from 125 to 114 pounds. She went to the World's Fair in September, and while there she had frequent and exhaustive pulmonary hemorrhages

The physician called in at the time pronounced the disease tuberculosis. She was brought home and kept closely confined to the house for fear of another hemorrhage. This fear was realized December 31, when the flow of blood was quite profuse. From this to the time of my seeing her her movements were still more restricted. Such in brief was the history given me, and from it one would infer that the infection had occurred in the winter of 1892-93, but on baring the breast for examination of the lungs a large scar just above the clavicle on the right side was seen, and on inquiry I learned that some three years before a gland had enlarged, suppurated and discharged, and other glands as large as hickory-nuts were found in the same region. In all human probability these glands were tuberculous, and the patient had been infected much earlier than the history previously given would indicate. Moist râles were heard over the apex on each side. No cavities could be detected. The sputum was small in amount, very ropy, and not purulent. The tubercle-bacilli were numerous. Guinea-pigs were inoculated with the sputum and died of tuberculosis after from six to ten weeks.

I made it a condition of my undertaking the case that Miss W. should walk to my office, a distance of about half a mile, every morning. The treatment was practically the same as in the preceding case. During the first two weeks the highest temperature observed was 99.5°. This sometimes occurred in the morning, more frequently at noon, and very seldom at night. Since the last of February the temperature has never been found above the normal. The bacilli gradually decreased in numbers. The last found was on March 28, when three bacilli were found on four cover-glasses. The patient continued to raise a little each morning until about

the first of July. Since then there has been no cough. The weight increased to 122 pounds. The enlarged glands have markedly decreased in size, but can still be felt. There has been no hemorrhage. There is impaired resonance over the apex of the left lung; the other seems normal.

CASE XXI.—Mrs. M., aged twenty-six, with one child, six years old, came to me November 15, 1893. She had been coughing and raising for a little more than a year. She had lost during this time about fifteen pounds. The sputum was small in amount, consisting principally of glairy mucus. Bacilli were found, but not more than half a dozen on each slide. The evening temperature stood quite uniformly at 99° . Mrs. M. had thirty drops of a one-half per cent. solution of nucleinic acid daily from the date mentioned to the last of June. Since that time she has had an occasional injection. The germs disappeared before January 15th, and have not reappeared. She weighs more now than she ever did, and there is no cough. The physical signs in this case were never sufficiently marked for me to attempt to define them, and after repeated examinations I could not positively say that there was any abnormality.

CASE XXII.—Mrs. R., a married woman, with three children, and who did washing for a living, came to me May 21, 1894. She had three years before weighed 140 pounds; then her weight was 106. She has done no washing, save for her own family, since I began to treat her, but she has done all of her own household work and has taken care of her children. She has walked to the office, a distance, during a large part of the time, of about one mile. The sputum in this case was at first abundant, but non-purulent. Bacilli were few. The upper lobe of the right lung was filled with moist râles. This

patient has had about thirty drops of a $\frac{1}{2}$ per cent. solution of nucleinic acid daily from the time of beginning treatment until the middle of October. The improvement was slow until recently, when it has progressed most rapidly. Since the middle of October she has had an injection every other day. The bacilli disappeared in July, and her weight is now 122 pounds. The cough has ceased, and there is no expectoration. No râles can be detected.

CASE XXIII.—Mrs. C., aged forty-five, a farmer's wife, and the mother of ten children, came for treatment May 17, 1894. She was coughing very much, but raised little. The sputum was non-purulent, and contained but few bacilli. During the previous six months she had been reduced from 130 to 115 pounds. She had treatment from May 17 to July 7; none since. In June the cough ceased, and she has raised nothing since. She now weighs 135 pounds.

CASE XXIV.—E. H., twenty-one years old, with no family history of tuberculosis, lived on a farm until seventeen years old, then went into a general merchandise store for two years. The past two years he has been book-keeper at Alexandria Bay, on the St. Lawrence. He has worked in-doors about sixteen hours per day. Four other employés of this firm have developed pulmonary tuberculosis. H. felt perfectly well until July 13, when he had a hemorrhage, losing about "a teacupful of blood." He quit work for three days, but had another hemorrhage September 3. He has had cough and night-sweats since the first hemorrhage. He came to Ann Arbor September 28, weighing 134 pounds. Cough and expectoration were slight; few bacilli were in the sputum. These had been detected by a physician at Alexandria Bay. There is slight dulness over both apices. This patient had in all thirty-four

injections of a 1 per cent. solution of nucleinic acid. The cough and night-sweats disappeared after the twelfth injection. No bacilli could be found after this in the small amount of fluid sputum brought up. The weight increased eight pounds.

These persons had no other medication, with the exceptions already stated, beside the nuclein.

These cases will be sufficient, I think, to enable me to draw the following conclusions:

(1.) In pulmonary tuberculosis which has progressed to the formation of cavities, nucleinic acid from yeast will not produce a cure. Unfortunately, these are the cases that we are expected to cure. These are the cases in which any proposed remedy for the disease will be tried, and I wish to state here most emphatically that I do not claim anything for nucleinic acid in these conditions. Indeed, I know, probably better than any one else, of how little value this agent is in these cases.

(2.) Even when the tuberculosis is of long standing, and when the extent of tissue involved is great, *so long as secondary infection with pyogenic germs has not occurred*, the proper use of the remedy may *retard* (I do not say arrest) the progress of the disease.

(3.) In initial cases of pulmonary tuberculosis, when there is no secondary infection, and when the area involved is small and the resistance of the patient not too much reduced, the proper employment of this agent may produce at least a temporary cure. I say "at least a temporary cure," because none of these cases has been under observation a sufficient length of time for me to say that the bacilli will not reappear.

(4.) In the few cases of urinary tuberculosis that I report in this paper the results have been remarkably satisfactory.

The results that I have secured so far encourage me to continue the work. There is no reason for supposing that the nucleinic acid obtained from yeast has any properties superior in a curative way to the nucleins contained in other substances. The number of nucleinic acids is limited only by the kinds of cells in existence, and I shall compare others with this one.

The early detection of tuberculosis is now a possible, not to say an easy, thing, but it is a lamentable fact that to many practising physicians it is an impossible thing. This will be the case so long as our most popular and most numerous attended medical schools fail to give any adequate individual instruction in bacteriology. The sputum of every patient who raises any should be examined for tubercle-bacilli, and urinary sediment containing pus, blood, or much epithelium should be similarly tested.

I must not close this paper without mentioning another point: I am convinced, especially from my experiments on animals, that nucleinic acid, improperly used, may do harm. It acts, as I have elsewhere shown, by stimulating the organs that elaborate the polynuclear corpuscles, and these may be over-stimulated. Nucleinic acid fails to be of service unless these cell-forming organs respond. They may fail to respond on account of lowered vitality, or they may be paralyzed, as it were, by an excessive dose of stimulant. The agent is not one to be used

indiscriminately. Already some physicians are supplying tuberculous patients with hypodermic syringes and solutions of nucleinic acid, and telling them to go ahead and treat themselves. Such practice as this may make the study of this subject result in a misfortune.

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